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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

October 3, 1988

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING[1]

October 3, 1988

The Recombinant DNA Advisory Committee (RAC) was convened for its thirty-ninth meeting at 9:00 a.m. on October 3, 1988, in Building 31C, Conference Room 6, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. Gerard J. McGarrity (Chair), presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Ronald M. Atlas	Robert P. Erickson	Gerald L. Musgrave
Michael F. Brewer	Martin F. Gellert	Paul E. Neiman
Donald C. Carner	Brian F. Mannix	David Pramer
James F. Childress	Robert D. McCreery	Monica Riley
Don B. Clewell	Gerard J. McGarrity	Jeffrey W. Roberts
Mitchell L. Cohen	R. Scott McIvor	Anne K. Vidaver
Bernard D. Davis	Richard C. Mulligan	Jay Moskowitz
Charles J. Epstein	Robert F. Murray	(Executive Secretary)

A committee roster is attached.

Ad hoc consultants:

William N. Kelley, University of Michigan Medical School
Robert B. Lanman, National Institutes of Health
Robert McKinney, National Institutes of Health
LeRoy Walters, Kennedy Institute for Ethics

Liaison representative:

Daniel P. Jones, National Endowment for the Humanities

[1]The RAC is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Non-voting agency representatives:

Patricia Hoben, DHHS, Office of the Assistant Secretary for Health
Phillip Harriman, National Science Foundation
Morris A. Levin, Environmental Protection Agency
Elizabeth A. Milewski, Environmental Protection Agency
George P. Shibley, Department of Agriculture
Sue A. Tolin, Department of Agriculture
Bruce Umminger, Department of State

National Institutes of Health staff:

Cindy Able, NCI
Paul Aebersold, NCI
W. French Anderson, NHLBI
Florence Antoine, NCI
Sheri Bernstein, NHLBI
R. Michael Blaese, NCI
Ken Cornetta, NHLBI
Ken Culver, NCI
Mark Damesym, NCI
David Dichek, NHLBI
Judith DiPietro, NHLBI
Martha Feller, NCI
Bernard Fox, NCI
Mary Ellen Franko, NCI
Scott Freeman, NHLBI
Jay Greenblatt, NCI
Ann Guiberson, NHLBI
Calvin Jackson, OD
Debbie Lenschow, NCI
Rachel Levinson, OD
Michael Lotze, NCI
Evelyn Karson, NHLBI
Attan Ksid, NCI
Richard Morgan, NHLBI
Daryl Muenchau, NHLBI
James Mule, NCI
Nga Nguyen, NHLBI
Steven Nuchtburger, NCI
Kristen Olsen, OD
Alan Price, OD
Steven Rosenberg, NCI
Morecki Shoshana, NCI
Liming Shu, NHLBI
Sabine Sturm, NHLBI
Joyce Tung, NHLBI
James Zwiebel, NHLBI

Others:

Terry Abshire, Hood College
Elizabeth L. Anderson, Environmental Protection Agency
Bruce Artim, Assistant Secretary of Health
Stanley Barban
James Barrett, Genetic Therapy, Inc.
Ira Carmen, University of Illinois
Chia Chen, Occupational Safety and Health Administration
Warren Cheston, Wistar Institute
Yawen Chiang, Genetic Therapy, Inc.
Joel Cohen, Agency for International Development
Robert Cook-Deegan, Office of Technology Assessment
Kimberly Dorsey, Hill and Knowlton
Marie A. Dray, Merck and Co., Inc.
Kathy Eisenhut, Hood College
Eric Flamm, Food and Drug Administration
Diane Flemming, Sterling Research Group
Denise Flickinger, Hood College
David E. Giamporcaro, McDermott, Will and Emery
Donna Hale, Hood College
Freddy Hoffman, Food and Drug Administration
Dorothy S. Jessup, Department of Agriculture
Attila Kadar, Food and Drug Administration
Gail Lavangie, Hood College
Warren Leary, New York Times
Jiayao Li, Embassy of the People's Republic of China
Carol Marcus-Sekura, Food and Drug Administration
Bob Moen, Genetic Therapy, Inc.
Satoshi Naito
Beverly Packard, Food and Drug Administration
John H. Payne, Department of Agriculture
Harvey S. Price
Joyce Rudick, Environmental Protection Agency
Carol Sardinha, Health Daily
Philip Sayre, Environmental Protection Agency
Alan Shipp, Association of American Medical Colleges
Janet Shoemaker, American Society for Microbiology
Jay Siegel, Food and Drug Administration
Joanne Silberner, U.S. News and World Report
Herbert Smith, Food and Drug Administration
Sharon Smith, Hood College
Robert Stevens, Department of Commerce
Garrett Strang, Pharmaceutical Manufacturers Association
Clarence E. Styron, Monsanto Company
Larry Thompson, Washington Post
Paul Tolstoshev, Genetic Therapy, Inc.
Odette Valabregue-Wurzburger, Lawyer
Joseph Van Houten, Schering-Plough Corporation
William J. Walsh, III, Currents International, Inc.
Rick Weiss, Science News
Lisa White, Blue Sheet
Rowland Wilkinson, Department of Defense
Pat Williams, Cancer Letter

I. CALL TO ORDER AND INTRODUCTORY REMARKS:

Dr. McGarrity, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to order at 9:00 a.m., October 3, 1988. The meeting was called pursuant to a Federal Register notice that, being 30 or more days prior to today's date, met requirements published in the NIH Guidelines for Research Involving Recombinant DNA Molecules. He stated that the meeting would remain open to the public for its entirety, and that he expected the meeting to conclude within one day.

Dr. McGarrity asked Dr. Gartland if a quorum was present and Dr. Gartland assured the Chair that a quorum was in attendance.

Dr. McGarrity noted that he intended to make every effort to abide by the distributed agenda with respect to time estimates for each item of business. He reminded the Committee that in recognizing persons for comments he would use the following order: primary and secondary reviewers on each item as set forth in the agenda; other members of RAC; ad hoc consultants to the RAC; NIH staff members; members of the public who had submitted written comments; and finally, other members of the public. He underlined that RAC was advisory to the Director of NIH; and in light of this, persons with minority opinions should voice them so as to provide Dr. Wyngaarden with the entire spectrum of opinions on a given topic. Dr. McGarrity then told the Committee that in all voting he would call first for the affirmative, then for the negative, and finally for abstentions. He emphasized that if any voting member felt compelled to abstain due to conflict of interest, that such member should notify the Chair so that the record could duly reflect such.

Dr. McGarrity then introduced the ad hoc consultants for the meeting: Dr. William Kelley, Chairman of the Department of Internal Medicine, University of Michigan Medical School; Mr. Robert Lanman, NIH Legal Advisor, Office of the General Counsel; and Dr. Robert McKinney, Director of the NIH Division of Safety.

Dr. McGarrity then made note of Mailings I and II, which were sent to members prior to the meeting. He also noted that some recently received materials were supplied at the table for each member.

Dr. McGarrity then introduced Dr. Jay Moskowitz, Associate Director for Science Policy and Legislation in the Office of the Director (OD), NIH, the new Acting Executive Secretary of the Committee, for his introductory remarks.

Dr. Moskowitz announced the administrative move of the Office of Recombinant DNA Activities (ORDA) to the Office of the Director. He said this change was in line with other administrative changes that focused on issues of public policy and science policy within OD. Among these changes were the establishment of an Office of AIDS Research and Office of Human Genome Research within the Office of the Director.

Dr. Moskowitz explained the organizational structure of the Office of Science Policy and Legislation which consists of the Division of Legislation, the Division of Planning and Evaluation, and the Science Policy Division in which ORDA is now located. The Science Policy Division deals with issues such as use of animals in research and animal welfare, fetal tissue research and use of fetal tissue for therapeutic purposes as well as tangential issues such as space medicine and the health of astronauts.

Dr. Moskowitz said his Office was in the process of developing updated job descriptions for Dr. Gartland's position as well as ORDA senior staff and expected formal advertisements to go out within the next month or two. He urged the Committee to aid in this search and asked that recommendations be brought to his attention for input into the personnel channels.

Dr. McGarrity announced that Dr. Gartland had left the Office of Recombinant DNA Activities to take a role in the extramural AIDS research program. He noted Dr. Gartland is known to many as "Mr. ORDA," and he stated he felt it appropriate to pay tribute to Dr. Gartland for his many years of dedication and service to the RAC.

Dr. McGarrity gave a brief synopsis of Dr. Gartland's academic and professional background, noting that he had come to NIH in the early 1970s to work with Dr. DeWitt Stetten in setting up the NIGMS Human Genetics Program. He remarked that the success of this program was due in part to Dr. Gartland's efforts in cell banking, a procedure which pooled researchers' resources into a central repository for all researchers to draw upon. In 1976, Dr. Donald Fredrickson appointed Dr. Gartland to head the Office of Recombinant DNA Activities, and since then Dr. Gartland has served in this capacity, at times representing the directors of the NIH institutes as well as the Director of NIH. Dr. Gartland was appointed Chairman of the U.S.-Japan Cooperative Program on Recombinant DNA, and has acted as liaison to many other countries. Dr. McGarrity noted Dr. Gartland received the NIH Director's Award, the NIAID Director's Award, and, in 1985, was the recipient of the Special Recognition Award from the U.S. Public Health Service.

Dr. McGarrity thanked Dr. Gartland, referring to him as "the ideal public servant scientist administrator," and said he was sad to see him leave but at the same time wished him luck in his new role in the Office of AIDS Research. He also thanked Dr. Moskowitz, Rachel Levinson, Becky Lawson, and the office staff for their efforts at maintaining order in this time of administrative changeover.

Dr. McGarrity then presented Dr. Gartland with a certificate inscribed as follows:

> "U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health presents to William J. Gartland, Jr., in grateful appreciation for his outstanding services as Executive Secretary of the Recombinant DNA Advisory Committee from 1976 to 1988, signed, Jay Moskowitz, Ph.D., Associate Director for Science Policy and Legislation, and James B. Wyngaarden, M.D., Director, National Institutes of Health."

Dr. Gartland accepted the certificate and said he owed a debt of gratitude to the founding fathers of the RAC concept, Drs. Donald Fredrickson and Joseph Perpich. He thanked the many RAC chairpersons over the years: DeWitt Stetten, Leon Jacobs, Jane Setlow, Ray Thornton, Kenneth Burns, Bob Mitchell, and Gary McGarrity. He thanked the entire office staff, Becky Lawson, Marianne Abbs, Karen Riggs, and Nancy Mulligan and the professional staff, especially Stanley Barban, and the many institute directors he had served under including Drs. Ruth Kirschstein, Richard Krause, Tony Fauci, and now Jay Moskowitz.

Dr. McGarrity called upon Mr. Brewer to present the minutes of the meeting of June 3, 1988.

II. APPROVAL OF THE MINUTES OF THE JUNE 3, 1988 MEETING:

Mr. Brewer said he had one correction to the minutes. On page 339 his name appeared as "Dr. Brewer," and it should have read "Mr. Brewer." Dr. Childress said he found the minutes to be very clear and accurate and that he would consult with staff about minor word changes. Mr. McCreery moved approval of the minutes and Mr. Brewer seconded the motion. Dr. McGarrity put the motion to a vote and it was unanimously accepted.

Dr. McGarrity then called on Dr. Walters, Chairman of the Human Gene Therapy Subcommittee, to present Agenda Item III, the Human Gene Transfer Proposal.

III. HUMAN GENE TRANSFER PROPOSAL (tabs 1332/II, 1333, 1337):

Dr. Walters circulated a chronology of the review process for the human gene transfer proposal submitted by Dr. W. French Anderson of the National Heart, Lung, and Blood Institute (NHLBI), Dr. Steven Rosenberg of the National Cancer Institutes (NCI), and Dr. Michael Blaese of NCI. He said the Human Gene Therapy Subcommittee of the RAC met on July 29, 1988, to consider the first human gene transfer proposal. He noted that this was the culmination of a long process that began in 1982 with the Presidential Commission on Bioethics report entitled "Splicing Life," which noted there was no current national review mechanism for considering such proposals. In 1983, the RAC began a process of developing such a review mechanism which has come to consist of three parts: review at the local level by local Institutional Review Boards (IRBs) for human subjects research and the local Institutional Biosafety Committee (IBC); mid-level review by the Human Gene Therapy Subcommittee and the RAC; and the final review by the NIH Director who accepts or rejects the recommendations of the RAC.

While the Human Gene Therapy Subcommittee was formed in 1983, it wasn't until 1987 that it was asked to examine a preliminary draft proposal. Dr. French Anderson, along with his colleagues, produced a state-of-the-art review of human gene therapy that dealt primarily with a genetic enzyme deficiency disorder, adenosine deaminase (ADA) deficiency, as a model for human gene therapy. Though never formally submitted as a clinical proposal, it did allow the Human Gene Therapy Subcommittee an opportunity to study the scientific literature, to become familiar with the technical and ethical issues surrounding gene therapy, and to receive comments from outside consultants.

In June 1988, the first clinical protocol involving gene transfer into humans was submitted to the local review bodies at NIH. The experiment dealt not with ADA deficiency, but with cancer, and was not a proposed treatment, but a diagnostic technique.

Dr. Walters presented a scientific summary of the protocol submitted:

> "Tumor infiltrating lymphocytes (TIL) would be isolated from a patient's tumor and grown in culture in the presence of interleukin-2 (IL-2). An aliquot of TIL would be removed at the time they reached log phase growth. The aliquot (representing no more than one-third of the total TIL population) would be incubated with the retroviral vector N2 (containing the gene coding for neomycin resistance, or Neo^R). This treated

aliquot would be grown in media contaning G418, a neomycin analog in which only those cells expressing the Neo^{R} gene can survive. The cells would be tested to insure that they are virus-free, have similar surface antigen patterns to the parent TIL population, and have not changed significantly in other properties (including continued dependence on exogenous IL-2 for growth). The treated aliquot would then be administered to the patient along with the bulk TIL population that would have been grown separately. The proportion of marked TIL in the final TIL population that would be returned to the patient would be between 5-30%. After administration, samples of blood, lymph nodes, and tumor biopsy material (already being obtained as part of the standard TIL protocol) would be tested for the presence of the Neo^{R} gene by PCR DNA analysis. The marked TIL would be recovered by growth of the tissue sample in IL-2 medium plus G418. The recovered cells would be studied for phenotypic and cytotoxic properties in order to attempt to learn why TIL immunotherapy is successful in some cases but not in others."

Dr. Walters then related the major events of the approximate four months since the proposal was first submitted to the Human Gene Therapy Subcommittee as follows:

June 10, 1988 Initial submission of what was technically an amendment of an approved clinical research project entitled "The Treatment of Patients with Advanced Cancer Using Cyclophosphamide, Interleukin-2 and Tumor Infiltrating Lymphocytes," to two NIH Clinical Research Subpanels (NCI and NHLBI).

June 15, 1988 Proposed amendment submitted to NIH Institutional Biosafety Committee.

June 20, 1988 Initial review of proposed amendment by NCI Clinical Research Subpanel which approved the amendment with the stipulation that the final version of the proposal be resubmitted to the Subpanel for final consideration, and offered ten recommendations for further amendment of the proposal.

June 21, 1988 NHLBI Clinical Research Subpanel reviewed the amendment and approved it with three stipulations including: (1) that the Subpanel deferred to the RAC on procedures to ensure no infectious viral particles remained in the preparation; (2) that final approval was contingent upon investigators'

report of ongoing experiments to demonstrate the N2 infected cells were representative of the major group of uninfected TIL cells; and (3) the informed consent form be revised.

July 5, 1988 — First mailing to Human Gene Therapy Subcommittee by ORDA.

July 13, 1988 — Review of proposed amendment by NIH IBC with approval conditional upon RAC approval and receipt of results from preliminary work in vivo in the mouse.

July 13, 1988 — Formal submission of proposed amendment to ORDA by Drs. Anderson, Blaese, and Rosenberg.

July 18, 1988 — Second mailing to Human Gene Therapy Subcommittee by ORDA.

July 29, 1988 — Human Gene Therapy Subcommittee review of proposed amended protocol and discussion with investigators which resulted in the Neiman motion to defer approval being accepted unanimously and agreement by the Subcommittee to review any additional data submitted by September 15, 1988.

Sept 16, 1988 — Submission of additional data to Dr. McGarrity by Drs. Anderson, Blaese, and Rosenberg.

Sept 20, 1988 — Mailing of additional data to members of the Human Gene Therapy Subcommittee.

Sept 29, 1988 — Conference call by members of Human Gene Therapy Subcommittee and consultants with unanimous judgment to defer approval reached by members and consultants to be presented at the October 3, 1988, RAC meeting.

In reporting on the July 29, 1988, meeting of the Subcommittee, Dr. Walters said the Human Gene Therapy Subcommittee wrestled with the issue of whether the protocol was, in reality, human gene therapy and whether it fell under the jurisdiction of the RAC and its Human Gene Therapy Subcommittee. After deliberation, it was decided the protocol was "very similar to human gene therapy," and that the Subcommittee should review it.

Dr. Walters said the Subcommittee unanimously approved a motion made by Dr. Neiman as follows:

> "consideration of the protocol be deferred until animal model testing is completed to include:

"1. Transfer of the vector to tumor infiltrating lymphocytes or TIL from a suitable murine tumor system;

"2. Detection of vector-marked TIL in recipient mice;

"3. Analysis of retroviral replication, tumorigenesis, and other undesirable effects in recipient mice;

"In addition, data should be presented demonstrating that:

"1. The human TIL that are marked by the vector are representative of the relevant cell populations, and;

"2. 'Dry run' tests with human TIL should be completed which demonstrate a lack of infectious helper virus by the most sensitive assays available."

Dr. Walters said that in the telephone conference call on September 29, 1988, the members and consultants unanimously agreed that additional information was still required in order to make a proper evaluation of this proposal. He called on Dr. Neiman to present the summary statement which resulted from the conference call.

Dr. Neiman distributed a written summary which he said represented both a summary statement and sense of the Subcommittee as a result of the July 29 and September 29, 1988, deliberations. He read the following statement:

"The sense of the Subcommittee and outside consultants is supportive of the general concept of the use of recombinant vectors in gene transfer procedures for marking somatic cells in humans as an aid to the development of important new advances in clinical research. Because such procedures are not done primarily to benefit the subject and may in fact be of no benefit to the individuals involved, proposals to carry out these experiments must be supported by a clear data base demonstrating if a specific procedure planned is safe and likely to yield knowledge of value.

"In the present case, knowledge likely to enhance further development of cancer immunotherapy with autologous human tumor infiltrating lymphocytes or TIL. Because the present proposal would be the first to involve human subjects and clearly sets precedence for proposals that follow, the Subcommittee views evaluation of the supporting data base as especially important.

"At its July 29 meeting, the Subcommittee agreed that the supporting data base for the proposal submitted by Drs. Anderson, Blaese, and Rosenberg was insufficient and recommended deferral of consideration of the proposal until this information was available. As an aid to the applicants, the Subcommittee listed the three points this data base should address with respect to animal testing and two additional issues with respect to the human TIL into which the vector has been introduced.

"The Subcommittee felt that provision of the requested data was well within the range of present technology and could be provided without unreasonably delaying the proposed clinical research.

"A telephone conference was held on September 29, 1988, by the Subcommittee to review additional data submitted by the applicants to determine whether or not there was now a data base sufficient to act on the proposal. Again, the conclusion of those participating in the telephone conference was that although some progress was made, we were not yet in possession of the requested information and our recommendation of July 29, 1988, therefore stands unchanged.

"As an aid to the applicants and the members of the Recombinant DNA Advisory Committee, the minutes of the telephone conference are appended to this summary which include evaluation of the specific data submitted by the applicants with respect to the points at issue raised by the Subcommittee."

Dr. Neiman said the minutes to which he referred were still in rough draft form. Many of the participants had not had a chance to review them, but they were provided for RAC members to get a flavor of the concerns on specific data.

Dr. McGarrity thanked Dr. Walters and Dr. Neiman for presenting the historical background and history of the proposal. He said he felt compelled to digress from normal procedures because a discussion of the issues with Drs. Anderson, Blaese, and Rosenberg would be more efficient in dealing with the many issues and called on Dr. Anderson to lead the discussion of the proposal.

Dr. Anderson said the primary issue of concern was raw data on a number of issues that were not present in the mailings. He said the reason why these data had not been supplied to the Subcommittee to date was because both Subcommittee meetings and the RAC meeting itself were open to the public. Releasing this

data in a public forum could jeopardize publication in both **The New England Journal of Medicine** and **Science.** Therefore, he suggested a compromise in the form of presenting the a summary of the data in slide format, rather than hand-outs, in order to avoid jeopardizing future publication. Dr. Anderson said this was an issue that NIH should resolve for future reviews of this nature.

Dr. Anderson noted that the Investigational New Drug (IND) submission that had been submitted to the Food and Drug Administration (FDA) was available for members of the RAC to look at the data in "off the record" portions of the meeting such as coffee breaks and at lunch on an individual basis.

Dr. Anderson said the protocol had been under review for six months and a great deal of critical evaluation of every aspect had been done. The proposal is one in which adults with advanced cancer will give their consent to a procedure with minimal risk which could provide invaluable information for improved cancer treatment. However, before this procedure is used in man, it must be shown that:

1. It is possible to insert a marker gene into human TIL and that the inserted gene will be expressed at a useful level;

2. Procedures used to introduce and select for expression of the exogenous gene do not significantly alter the transduced cell;

3. The proposed procedures have a reasonable chance of success based on animal feasibility studies;

4. The proposed protocol does not add a significant new threat to the patient;

5. The gene transfer procedure does not present a risk to health care personnel or to the public in general.

Dr. Anderson said all of these points would be addressed in presentations and data addressing each point would be made available where possible. Where proprietary data were concerned, summary information would be presented. He said the five points had been addressed satisfactorily. It was determined that: insertion and expression of the marker gene in TIL could be accomplished; that the marked TIL are not significantly altered; that detection of marked cells in animal models, including murine models, showed there was a reasonable chance for success of the procedure; and that there is low risk to the patient and no risk to the public.

Dr. Anderson then introduced Dr. Rosenberg to explain why he felt that the execution of this protocol would improve cancer immunotherapy.

Dr. Rosenberg said he would present an overview of where this protocol would fit into an 11-year effort to develop new treatments for cancer patients. He noted last year 485,000 Americans died of cancer, and one out of every 6 Americans now alive will die of cancer if no new treatment modalities are developed. The three treatment modalities currently in use are: surgery, radiation therapy, and chemotherapy. He noted about half of all cancers can be cured by appropriate application of these modalities, but with the high incidence of the disease, there are still approximately one-half million cancer deaths each year.

Dr. Rosenberg said one new modality is biologic therapy or immunotherapy, i.e., utilizing the body's own immune defense mechanisms to treat cancer. The particular immunotherapy being investigated by Dr. Rosenberg is called adoptive or cellular immunotherapy whereby a patient's own immune lymphoid cells are taken out of the body and induced to recognize and destroy cancer cells and later reintroduced into the body as an immune reagent.

Dr. Rosenberg defined "adoptive immunotherapy" as "the transfer to the tumor-bearing host of active immunologic reagents with anti-tumor reactivity that can mediate directly or indirectly anti-tumor effects." A limitation to adoptive immunotherapy is the inability to generate sufficient numbers of cells with appropriate anti-tumor reactivity for transfer to tumor-bearing patients. The TIL protocol represents the first method for isolating and employing lymphocytes that will react with specific tumor antigens.

Dr. Rosenberg said early efforts in adoptive immunotherapy were derived from studies that showed that lymphokine-activated killer cells (LAK cells) with anti-tumor reactivity could be formed by incubating lymphocytes, in vitro, with interleukin-2 (IL-2) to generate cells capable of lysing fresh tumor cells and reintroducing them into the host. This method has been used to treat over 300 patients and has proven useful in regression of tumor growth in some cases of advanced cancer. Dr. Rosenberg emphasized that these experiments were conducted in patients with advanced metastatic cancer who had failed all other therapies available and who had been sent home to die. The same population will participate in the proposed TIL experiment.

Dr. Rosenberg said two-thirds of patients did not respond to the LAK treatment. As part of a continuous effort to improve adoptive immunotherapy, it was observed that lymphoid cells infiltrating a growing tumor had unusual properties and a

technique was developed to isolate these tumor infiltrating lymphocytes. Tumor infiltrating lymphocytes (TIL) can be grown by culturing single cell suspensions from tumors in a medium containing IL-2. In 2-3 weeks, a pure culture of lymphocytes derived from the original suspension remains, having outgrown the tumor cells.

Dr. Rosenberg noted that in experiments published in **Science** utilizing an experimental animal model, the therapeutic properties of such TIL were 100 times more potent than LAK cells and were shown to produce a 100% reduction in metastases. These results became the basis for considering trials in humans. Experiments were then undertaken to grow TIL from patients with metastatic cancer. It was found that they could be grown from virtually any kind of tumor, and that they had a unique reactivity with the patient's cancer but not with the patient's normal cells. At the same time, these TIL had no reactivity with other patient's cancers. The experiments showed that TIL from a patient lysed his tumor efficiently but did not lyse his fibroblasts, B cells, normal lymphoid cell lines or any other allogeneic tumor, representing the best evidence available to date that patients with growing cancers do mount immunologic reactions against their own tumors.

With this background, the FDA granted permission to begin a trial with TIL, a report of which has been submitted for publication to **The New England Journal of Medicine** and will probably appear soon. Dr. Rosenberg summarized the results by stating that of the first 20 melanoma patients treated, 15 of whom had not previously received TIL therapy, there was a 50 percent reduction in tumor mass in 9 of the first 15 patients, and one patient had experienced a complete regression. The majority of these patients had only received a single course of therapy, but multiple course therapy has been approved recently by the FDA. Dr. Rosenberg said that 5 patients who had previously failed treatment with LAK cells were treated in an effort to gain information about TIL potency and 2 of these patients had good objective regressions, an indication of increased efficiency of this approach.

Dr. Rosenberg presented individual case information on three patients and summarized that the experiments show that it is possible to utilize the immune system to mediate regression of growing cancers, but that the treatment is not perfect in view of the fact that less than half of patients respond. Further, there are toxicities associated with the treatment and much more must be learned about its mechanisms of action. One major goal is to identify correlates between classes of lymphoid cells that cause regression and their *in vivo* activities. Further information concerning long-term survival of human TIL is also needed. Dr. Rosenberg also noted that there was no existing technique

other than utilization of indium-111 labeled autologous TIL to monitor trafficking of both the lymphoid cells to tumor deposits, or to other parts of the reticuloendothelial system.

Dr. Rosenberg said that if cells could be produced incorporating genes for other cytokines such as tumor necrosis factor or alpha-interferon, they could be utilized in the mechanism of cancer killing, thus, dramatically improving the effectiveness of this treatment approach. He hoped to return to the RAC and ask permission to introduce genes with therapeutic potential into humans to improve this therapy.

Dr. Rosenberg related that in the search for new cancer treatments, Phase I protocols that have a 10-20 percent treatment-related mortality are being considered daily by clinical research committees. Because of the low additional risk posed by the gene transfer procedure, Dr. Rosenberg felt that it was worthy of careful consideration and approval.

Dr. Neiman asked if a dose-response curve had been constructed, based on the number of TIL administered to the patients. Dr. Rosenberg said they intended to administer as many cells as can be grown in 3-4 weeks and attempt to transfer somewhere between one and 4 X 10^{11} of these TILs. His response to Dr. Neiman's question was that a correlation between number of cells transferred and anti-tumor response has not been established in the small number of patients treated to date.

Dr. Rosenberg then called on Dr. Blaese to present further information on the protocol.

Dr. Blaese said that when he began his work in gene transfer technology, its use in the treatment of cancer was not anticipated. It was thought more likely that the first diseases to be dealt with would be genetic diseases such as adenosine deaminase deficiency (ADA). However, as work with lymphocytes in culture progressed, it rapidly became apparent that one of the attractive features of these cells was their capacity to act as cellular vehicles for gene therapy. The protocol now before the RAC was developed as a result of such experimentation.

The investigators seek to answer the following key questions:

1. How long do the TIL persist <u>in vivo</u>?

2. Where are they located in the body?

3. Does longevity or location correlate with clinical effect?

4. Is it possible to recover the TIL?

5. What functional characteristics of the TIL define their ability to localize tumor or distant sites?

6. Is there a correlation between localization, function and clinical efficacy?

Dr. Blaese said the protocol calls for labeling TIL with the retroviral vector N2 containing the Neo^R (neomycin resistance) gene. Investigators will label less than 50 percent of the patient's harvested TIL population so that removal of cells for retroviral marking will not interfere with the therapeutic process. The N2-transduced TIL will be reinfused at the time of standard therapy. They will then biopsy tumor nodules and other tissues at intervals and measure the vector presence by detection of the inserted gene. These biopsied samples will then be cultured and the TIL regrown with the Neo^R gene to recover cells infused initially for analysis of their functional phenotype and correlation to response to treatment.

Dr. Blaese explained that an advantage of using such marker genes would be that they provide properties that exogenous labels cannot provide for answering many of the questions stated above. Further, a gene label would not leach away from the original cell as is the case with many radioactive labels. Also, radioactive labels are lost as soon as a cell dies and do not become sequestered or reutilized marking other cells or tissues. The genetic label is not diluted out as TIL proliferate in the patient with continued administration of IL-2. The gene marker should permit specific recovery of the marked cells at a later date, thus permitting recharacterization of cells after they have spent variable periods of time in the patient.

Dr. Blaese explained the methods for performing the cell culture and infusion in detail. He described experiments that had been performed using the N2 retroviral vector which demonstrated that the marker gene could be introduced into human TIL and expressed at a useful level.

Dr. Blaese said the N2 vector had been introduced into TIL populations obtained from 15 patients, including 6 patients in whom the entire procedure being proposed, short of reinfusion, had been followed. The results of this experiment showed an infection efficiency of approximately 10 percent. The introduction of the vector; selection in G418 medium, a neomycin analog; and the presence of the marker gene, did not interfere with the capacity of the cell for normal growth compared to the regular TIL population in these patients.

To answer the question of whether the marked TIL were significantly altered by the process of inserting the gene, Dr. Blaese explained they had removed marked cells and analyzed them for cell surface phenotype changes. Using a fluorescence activated cell sorter, they found no significant alterations in phenotype over time in culture although some drifting and maturation of phenotype did occur which is normal in cultured cells over long periods of time.

Dr. Blaese said another experiment was performed to discover whether absence of changes in cell surface phenotype may be reflective of other changes occurring, such as cytotoxicity. This was performed by looking at the ability to kill autologous tumor. TIL samples from four of the six patients studied were non-cytotoxic and did not acquire cytotoxic activity after gene insertion. Two of the patients TIL were cytotoxic against the autologous tumor but not against other targets both before and after vector insertion and selection. So, no changes in cell cytotoxic activity has been seen. Cytokine production was also looked at and found to be unaffected by vector insertion and selection, as was T cell receptor specificity and heterogeneity. Therefore, Dr. Blaese concluded that some modifications occur in some TIL populations; however, in the vast majority of cases the TIL are not significantly altered by the process of inserting the genes and selecting for expression of Neo^R.

Dr. Blaese described studies undertaken to detect the marked cells in animal models. He summarized data from one such model, the nude mouse. Normal mice were immunized with sperm whale myoglobin. The lymphoid tissues were then removed and expanded in culture. The SAX vector (an N2 based vector) was used to carry two genes: one coding for neomycin resistance, the other coding for human ADA, into these lymphoid cells. Then the tissues were reinfused into nude mice and the animals were analyzed at various times for presence of the inserted gene. Twenty-three days after receiving the cells containing these genes, blood in 5 animals was found to be positive for vector DNA. Furthermore in one animal, after 37 days, both blood and spleen were analyzed and the spleen was directly positive for vector DNA. After growing both spleen and white blood cells in culture, they were found to be G418 resistant and to express human ADA. The longest surviving animal transduced with the SAX vector is positive for DNA in the spleen 105 days after cell transfer.

Dr. Blaese then presented the results of experiments in a murine system using SAX-transduced TILs recovered from lymphoid tissues. He also described an experiment in primates that was conducted using the N2 vector to transduce T lymphocytes in culture. Tetanus toxoid was used to stimulate cell proliferation after which the lymphocytes were reinfused intraperitoneally. Cells

recovered from lymph node biopsies contained the gene marker whereas the peripheral blood was negative for gene expression.

Dr. Blaese then discussed the safety issues related to the TIL experiments. He said one question raised by the Human Gene Therapy Subcommittee had to do with the presence of infectious helper virus or replication competent retrovirus in the population of cells as well as in the vector that is to be introduced. Dr. Blaese said although he believed there was no evidence that infectious helper virus is present either in the initial population or in the TIL populations that will be given back to the patients, their presence can be tested; and that infectious virus will not be given back to patients.

Dr. Blaese said another question related to whether introducing the gene into TIL would change their characteristics or induce some transformation event that would make their growth characteristics different from normal TIL. He presented data on the proliferation of TIL populations over time, measuring counts per minute of thymidine incorporation, with or without IL-2. In the presence of IL-2, marked TIL proliferated well but did not proliferate if IL-2 was removed, demonstrating the absence of autonomously growing cells in these cultures. Furthermore, they inserted vectors into TIL in culture, and found that in the absence of IL-2, no viable cells could be detected after 2-3 weeks, showing that no transformation event had been induced that might result in IL-2 independent cells.

Dr. Mulligan asked how many mice had been tested in the murine experiment. Dr. Blaese said six animals were used in the first experiment. Further, there was a second series of experiments with mouse TIL that wasn't shown, using a similar protocol where lymphoid, lung, spleen, kidney, and liver tissues were recovered at 1 hour, 6 hours, 26 hours, 72 hours, 5 days, 7 days, 9 days, and 11 days after transfer of TIL. In this experiment, the strongest signals obtained so far have been in the lung at 1 and 6 hours and in the liver at 24 hours.

Dr. Kelley asked if there were other species where TIL had been demonstrated that might serve as a model for man. Dr. Rosenberg replied that it had only been done in mouse and man, but that TIL from spontaneous cancers in other species could be looked at.

Dr. McGarrity announced the morning coffee break, and then resumed discussion with Dr. Anderson's presentation.
Dr. McGarrity reiterated the tabs relevant to the agenda item and asked Dr. Anderson to continue.

Dr. Anderson noted that questioning had been vigorous and that members of the Human Gene Therapy Subcommittee, some of whom are his closest competitors, also had scrutinized the protocol at

every step. He said he believed this was good so that the public would know there had been careful evaluation at every step. He noted, however, the RAC is not an investigative committee and he did not believe the purpose of the RAC was to question whether he knew how to do an experiment with retroviruses, whether Dr. Blaese knew how to grow T cells, or whether Dr. Rosenberg knew how to treat cancer, but that its function was to protect the public safety. The presentation, he said, was intended to demonstrate that there are extensive data showing both the feasibility of the protocol as well as its safety. He added that further information was available to members of the RAC in the IND application being submitted to the FDA.

Dr. Anderson said data had been presented to demonstrate the answers to the first three questions that he identified earlier. The fourth question was whether or not the protocol represented a significant new threat to the patient. To answer this, he proceeded to offer quantitative data to show that the TIL contain no infectious viral particles.

Dr. Anderson said he employed the S+/L- (sarcoma positive/ leukemia negative) assay, using a supernatant from 4070A, a wild type murine amphotropic virus to detect infectious viral particles. This assay can be quantitated to detect the presence of a single infectious viral particle in supernatant diluted by $3x10^{-6}$ or $3.3x10^{-7}$. He noted that a paper describing this procedure was being submitted for publication in **Virological Methods**. A 3T3 amplification test is performed in order to double-check the procedure. In this assay, various supernatants are plated directly onto NIH 3T3 cells, which are very permissive for replication of retrovirus, then grown for a week until the whole plate is covered, and examined for foci at one and three weeks.

Dr. Anderson said experiments were performed in which the supernatant was intentionally contaminated in order to titer infectious viral particles. He showed data from three patients demonstrating the absence of helper virus in transduced TIL. When samples were intentionally contaminated, usually only about 6 foci could be detected. The highest number of foci that could be detected was 40 or a titer of $2\text{-}5x10^{5}$ causing him to conclude that N2-transduced human TIL are generally virus-free. Even when intentionally infected, human TIL support murine amphotropic virus only at an extremely low titer and some human TIL don't support it at all. He noted that the bulk of supporting data for this could be found in the IND which was submitted to the FDA.

Dr. Anderson presented results of polymerase chain reaction (PCR) assays looking for DNA from the packaging cell line. Using a series of primers, marked and unmarked TIL from 3 patients were analyzed. Although PCR is difficult to quantitate, it is

possible to detect one infected cell in 10,000 unmarked cells. He concluded by saying, "if we ever find a human TIL which has an infectious viral particle, we simply won't use it."

Describing data on the reverse transcriptase assays, Dr. Anderson commented that it is not very sensitive past dilutions of 10^{-3}. In conclusion, Dr. Anderson listed the following assays for replication competent retrovirus: S+/L-, 3T3 amplification at 1 and 3 weeks, PCR for envelope sequences and viral genome, and, in addition, S+/L- performed by a commercial laboratory.

Dr. Mulligan asked if in the helper assay, which can detect a titer of $3X10^5$, whether the presence of a recombinant at a titer 10-fold higher did not present problems with assay sensitivity. Dr. Anderson replied that in such a case, 1:10-fold dilutions could be made to bring the test sample into the proper sensitivity range for the assay. Further, in response to continued questioning, Dr. Anderson said the point was that they were testing human TIL which have titers of zero, 1, 5, or 10. Dr. Mulligan said that he felt it necessary to see confirmatory data on the sensitivity of the helper assay, to which Dr. Anderson replied that the assay was sensitive and could detect one viral particle up to as high as one could go and, therefore, was a non-issue. He said he, as well as other cancer researchers, feel that the added risk to cancer patients of using marked cells was slight. He noted that in many cases, these same patients were enrolled in Phase I trials of new chemotherapeutic agents with no greater problems or benefit but with far greater risk. He said, "This is a safe procedure. It is a straightforward procedure."

Dr. McIvor pointed out that the Human Gene Therapy Subcommittee had not seen much of the data that had been presented at today's meeting. Dr. Anderson confirmed that the Subcommittee had been told the data would be supplied but, as he pointed out earlier, that was prior to the conversation over publication. He noted that this was the first time the bulk of this data had been presented.

Dr. Anderson continued by presenting data on in vivo safety studies in monkeys that were inoculated with large amounts of murine amphotropic retroviral particles after being immunosuppressed with no evidence of clinical illness as a result.

Insofar as infection of healthcare workers, Dr. Anderson said there was some concern over possible needlesticks. He said experiments were done, again in immunosuppressed monkeys, taking skin fibroblasts and chronically infecting them so they were shedding virus and reinserting them in the animal until a retroviremic state could be achieved. Virus could be

demonstrated in the lymph nodes for 2-3 weeks but retroviremia disappeared after two days. Further tests were done on stool, urine, and saliva; and all were negative. At 84 days, all specimens were negative, but there was a persistent antibody response.

Dr. McGarrity said the word "infected" was not a good choice to use when discussing insertion of the gene coding for neomycin resistance. Dr. Anderson said the word "transduced" was used in the IND and is a better word.

Dr. McGarrity then called on Dr. Walters for his comments. Dr. Walters underscored the point that comments (tab 1341) received by Dr. Albert Owens (of the Johns Hopkins Oncology Center and consultant to the Human Gene Therapy Subcommittee) were based on his receipt of the new materials only. Dr. Owens did not have available all the materials the Subcommittee had received. However, it was made clear to all members of the Subcommittee that Dr. Owens was satisfied with the materials and was able to base his judgment on them.

Dr. Erickson said he was not working in this field and further was not at the July 29 meeting of the Subcommittee but was party to the conference call. He was sympathetic to the Subcommittee's desire for quantitative data which had not been presented until today's meeting. He pointed out that he did not feel it was the purview of the RAC to assess the scientific quality of the experiment but to be more concerned with the safety issues, and much of this hinged on whether the S+/L- assay was the best way to detect the retrovirus. He said he was not sure where he stood on this issue, because he had just been presented with the data.

Dr. Kelley said his feeling was the experiment had no benefit to the individual patient in which it was to be carried out and therefore this exacerbated the risk issue. He said the long-term goals were very important and had the potential to be extremely important therapeutic modalities. Because of these reasons, the animal model data was important. He expressed concern that the only data presented on animal models were obtained from one mouse. Dr. Kelley was concerned that these were not enough data on which to judge the experiment and that additional studies in mice needed to be performed before the technique could be used in man.

Dr. Mulligan said he did not believe enough data had been presented on the issue of infectivity and he did not think it fair to ask the Committee to make a decision without having had time to look at the data and to discuss the assay sensitivity. He said tremendous progress had been made on data collection and that it could be approved shortly.

Dr. Neiman said he felt the Committee was trying to conduct the review in a fashion that sets the standards for future reviews, and this was not an attempt to delay important clinical research. He said the quantitative data presented showed considerable progress had been made, but the Subcommittee had deferred making a recommendation to the RAC pending submission of data to the Subcommittee. He said the issues central to the question of safety needed to be resolved. The data on retroviral replication, tumorigenesis, and undesirable effects on the recipient seemed to be limited by sensitivity of the assays as presented by Dr. Anderson. He said a more sensitive method would be to see if small numbers of viral particles could be amplified in a whole animal and cause viremia, and such data had still not been supplied.

Dr. Anderson said Moloney murine retrovirus could not used in adult mice, but it has been done in newborn mice. Although there was considerable data, it was irrelevant.

Dr. Neiman said he was not convinced there were no in vivo assays for amplification of small numbers of viral particles in an experimental animal comparable to humans, but progress was being made. However, he said, a meeting of the RAC was not the place where a final decision could be reached.

Dr. Epstein asked if it could be determined that after TIL are put back into a patient and later removed from tumor, what fraction of the lymphocytes reisolated are in fact the marked population. Dr. Anderson replied this was a question now being asked and had not yet been determined. Dr. Epstein asked what protocol would be used to determine this. Dr. Rosenberg replied that the first question to be answered is whether the location of these transferred cells correlated with a clinical effect. The qualitative issue could be answered by stimulating all lymphocytes in a tissue subpopulation with lectin, growing them in IL-2, and looking under G418 selection to see if the marked cells were present.

Dr. Rosenberg replied to Dr. Kelley's assertion that the treatment had no potential benefit to the patient who is actually receiving the transferred cells. He said that this immediate procedure may not be therapeutic. However, if it were found that the transferred cells persisted in draining lymph nodes only in patients who respond, then the transduced cells from the lymph nodes could be isolated and their properties determined. He gave the example that if they were the only cells secreting tumor necrosis factor (TNF), then the gene coding for TNF could be used therapeutically in subsequent patients to produce therapeutically effective subpopulations of cells. Dr. Rosenberg stressed that delays in such experimentation would have deleterious effects on cancer treatment and he expressed a desire that the RAC vote at

this meeting to enable at least the initial experiments to go forward. Dr. Anderson underlined that there were further reviews the experiments must undergo and that a delay in voting would in fact be amplified by causing further delays in other parts of the review process.

Dr. Epstein said he was not sure whether an animal model was really required for the proposed experiment since it would not matter whether the results were positive or negative. However, he said he was disturbed by the fact that the RAC was being put into the position of passing on an experiment in which data had been deliberately withheld on the basis of claiming that release of the data would jeopardize publication. He asked whether data presented today were on or off the record; and if they were off the record, how this affected their usage in the ultimate decision to approve or not approve the protocol.

Dr. McGarrity noted that Mr. Lanman, the NIH Legal Advisor, was not present; but in his opinion, the data were on the record insofar as the RAC was concerned. However, presentation of the data here did not constitute a "public disclosure." Dr. Anderson concurred and stated that all data presented at the meeting were on the record.

Dr. McGarrity noted that references to the RAC as a "regulatory committee" were not totally accurate. In fact, by definition, the RAC is advisory to the Director of NIH but in reality could be construed to be a de facto regulatory body.

Dr. McIvor said he had three concerns:

1. The ability of the PCR assay to detect virus sequences from the reinfused cells;

2. The utilization of the S+/L- assay to detect replication competent virus; and

3. The use of an animal model in which the N2 vector could not infect the murine TIL.

Dr. McIvor said in the case of the two assays, he felt the Subcommittee should have a chance to evaluate the current status of these and to look at the data presented before making a recommendation. Further, on the animal model, he asked whether it were possible to extrapolate the findings in the murine model to the human because of the carefully controlled experimental approach to the model.

Dr. Rosenberg explained there are four major differences in mouse and human TIL. All mouse TIL are CD8+ [one class of lymphocytes defined by the presence of CD8 cell surface markers], and CD4+

TIL cannot be grown in the mouse, yet they are therapeutically effective. Humans can have both CD4+ and CD8+ TIL. Dramatic anti-tumor responses have been achieved using the CD4+ TIL which can't be grown in the mouse, despite their having therapeutic effects. Therefore, Dr. Rosenberg said results in an animal model would not be predictive of results in man.

Dr. McIvor then asked how long murine TIL persisted in vivo, and where they persist in lymph nodes, tumor, or the bloodstream. Dr. Rosenberg replied that the questions had not yet been answered. However, given the differences between murine TIL and human TIL and differences between transplanted tumors in mice and spontaneous tumors in man, the answers in the animal model would still have to be corroborated in man. He noted cytokine research where interleukin-4 will stimulate LAK cells in mice while inhibiting LAK cell production in man. Dr. McIvor said he thought this was the kind of discussion that needed to take place within the Subcommittee.

Dr. Anderson noted that at the break he had been asked "what's the rush?" He said he thought it would be useful for members of the Subcommittee or the RAC to visit the Oncology Service of the NCI at the NIH Clinical Center to talk with patients dying of cancer and ask them the same question.

Dr. Murray noted that in the areas of sickle cell disease research and in vitro fertilization, where no animal models existed, little progress could have been made if it had been determined to wait for an appropriate animal model. In fact, progress had been achieved by taking risks. He said he felt the same could be done with this protocol. He likened this to early work with recombinant DNA where extra precautions were taken until the relative safety of the procedures became clear. He said he favored allowing "cautious proceeding" but asking at the same time for data in animal studies. He said, "I think we're placing too much emphasis on the animal experimentation, not that they're not important, and we have to pay more attention to the human situation."

Dr. McGarrity asked if he was correct in assuming that when safety was being talked about that it referred to: (1) safety in the patient who may be living for 2 months or 3 months; or (2) safety in the patient who may be cured and then carry the retroviral vector over an extended period of time. Dr. Mulligan said both of these were safety concerns. Dr. Murray said some cancer chemotherapy regimens are very toxic and may place the patient at risk for cancer or other disease, but may afford them the chance to be cured of the primary disease.

Dr. Kelley said this analogy didn't fit because in the protocol being proposed, no benefit will accrue to the patient whereas the

cancer patient benefits directly from chemotherapy. He said he felt the risk-benefit ratio is important to the patient and must be considered.

Dr. Rosenberg noted that Phase I studies of chemotherapeutic agents are routinely performed without potential for patient benefit, and the potential benefit to patients from this kind of protocol probably exceeds that of most Phase I studies in progress in cancer research.

Dr. Musgrave asked Dr. Kelley if any public health risks were found, other than the ones mentioned previously with regard to health workers, and whether there was any incremental risk of mortality to the patients. Dr. Kelley said these were the questions being asked, but he did not think the investigators knew the risks. Further, Dr. Musgrave asked if cutting the life expectancy of a patient by 30 days was significant in this group of terminal patients. Dr. Kelley answered that he was not an expert in the area of ethics, but others in the room were better able to answer such a question. Dr. Anderson said there were three years of data in primates showing that this vector has not been responsible for any pathology.

Dr. Cohen said he thought the experiment was logical; because, contrary to inserting something toxic, it was merely inserting a marker, that will aid in answering many questions on the consequences of human gene therapy. With respect to the individual host receiving the therapy, he said the development of further illness down the road was not important. The patients will have a very short life expectancy. However, the issue of future retroviral infections is a valid public health concern. Therefore, he asked whether people can be infected with this particular helper virus.

Dr. Anderson said the vector is a Moloney murine retrovirus which can infect the host, however, it is packaged in a murine amphotropic envelope. Many human cells are infected and can maintain a replication cycle. However, there is a question as to the danger that might result from putting a small amount of virus into a human. In order to examine this possibility, a monkey was infected with a small amount of viral supernatant which was intentionally contaminated with replication competent virus as well as 4070A wild type murine amphotropic virus--a total of 10^7 viral particles--and nothing happened. After 17 months, the animal has shown no indication of a problem. A second monkey was given a larger bolus injection in the same manner and a third had 22 percent of its blood volume replaced with pure viral supernatant. This animal exhibited transient lymphadenopathy from day 7 to day 14 with no ability to grow virus from the lymph nodes and no indication that anything other than viral antigens were present.

Dr. Anderson said they repeated the experiments in immunosuppressed monkeys with essentially the same results and even went a step further in infecting fibroblasts and reinserting them into monkeys. At 84 days there is no evidence anywhere of any clinical symptom and no evidence of virus.

Dr. Cohen asked whether the sensitivity of the assay to detect helper virus was significantly below what is a potentially infectious dose of the virus, Dr. Anderson replied it was 8 orders of magnitude better than needed to assure detection.

Dr. Davis said he was uncomfortable with the situation and perhaps some philosophy needed to be discussed. He said there has always been a principle in medicine that the sicker the patient, the higher the risk you are entitled to take in experimenting on the patient. He said Dr. Kelley's statements regarding subjecting patients to substantial risk were contrary to this principle in that they have only a 2-3 month life expectancy. Dr. Davis thought this seemed to be nitpicking over inconsequential levels of sensitivity in assaying for the virus. He could understand delaying this protocol if there were indeed threats to safety of medical personnel or the general public or a really substantial risk to the patient. However, he felt the RAC were acting as a study section by evaluating the quality of the proposal. He did not see this as the purview of the RAC. He was quite convinced that there were no risks that would justify withholding permission to carry out an experiment which everyone agreed would provide valuable information if successful.

Dr. Davis said he understood Dr. McIvor's questions on the animal experimentation but success in an animal model would not make human experimentation unnecessary. Moreover, there was not going to be any animal experiment that could be a replacement for human experiments on the basis of the data presented in support of this protocol.

Dr. Walters outlined the procedural aspects of the situation noting the Subcommittee was to have had the entire protocol 12-14 weeks before a regularly scheduled meeting, but they had received the materials less than 4 weeks prior to the July 29, 1988 meeting. Despite the late arrival of information, the meeting went forward and a conference call was scheduled for September 29, 1988, to take care of remaining questions before the October meeting of the RAC. He noted that the Subcommittee had telescoped an anticipated longer process into a much shorter timeframe in an effort to be responsive to the investigators.

Dr. Childress said he found the risk-benefit ratio acceptable and felt that the problem was really the issue of the use of gene markers versus a therapeutic gene transfer protocol which is of

concern to both the Subcommittee and the RAC. Many people did not feel this protocol should have come to the Subcommittee and that concern should not be over risk but over the future of gene therapy. He said he was comfortable with recommending that the study go forward but was uncomfortable that the process had become truncated which could set the tone for future protocol submissions to both the Human Gene Therapy Subcommittee and the RAC.

Dr. Childress added that he was interested in whether there was a way to speed the process up without having to wait for another formal meeting of the Subcommittee or the RAC.

Mr. Carner moved that the procedure be approved as presented with the provision that it be limited to 10 patients, each of whom has a life expectancy not to exceed 90 days, and each of whom consents to participation after having a full understanding of what he or she is accepting.

The motion was seconded, and Dr. McGarrity offered the motion to the floor for discussion. Dr. Davis said there was a gap between the assay sensitivity issue and the risk issue but that he didn't feel it justified holding the protocol up. He said he was not comfortable with Dr. Anderson's emotional appeal but that it could not be disregarded. Further, he said this protocol should not be viewed as precedent-setting, and future cases will be judged on their own merits.

Dr. Murray said because of the close call and difference of opinion as to whether this proposal should even come before the Subcommittee and the RAC, it should be deemed a "special case," since it is not gene therapy in the classical sense and agreed that it would not constitute precedent for future protocol consideration.

Mr. McCreery called the question. Dr. McGarrity put the motion to call the question to a vote. The motion passed by a vote of 11 in favor, 9 opposed, and no abstentions.

Dr. McGarrity then put Mr. Carner's motion to a vote. The motion passed by a vote of 16 in favor, 5 opposed, and no abstentions.

Dr. McGarrity thanked all presenters, Subcommittee members, and RAC members for the tremendous amount of time they had expended on this item. He then called on Dr. Murray who asked the investigators to provide the Subcommittee with the data and to keep them informed as to the progress of the protocol.
Dr. Anderson responded that he would be happy to supply the data and the IND provided it was done in a manner that did not make it available to the press.

Dr. McGarrity noted that there was a procedure for holding a closed meeting, but that it had to be announced in the Federal Register within the proscribed notification period. Such a procedure may be used in the future for more complicated proposals so that they can be handled expeditiously. He then recessed the Committee for lunch, to reconvene at 1:45 p.m., the same day.

Dr. McGarrity opened the afternoon session by once again thanking the Human Gene Therapy Subcommittee for its time and dedication in reviewing the human gene transfer proposal. Mr. Brewer added that he believed the result of the deliberations on the human gene transfer proposal showed a balance of the concerns on all sides of the issues. He said he didn't consider the decision precedent-setting in any way, and he viewed it as a stand-alone case reviewed on its merits. He noted that in the future there will be proposals that will be more complex and will require the kind of scrutiny exhibited in the Subcommittee and at this meeting.

Dr. McGarrity then called on Dr. Cohen to present the next agenda item.

IV. PROPOSED AMENDMENT OF SECTION I-C OF THE NIH GUIDELINES (TABS 1332/I, 1334, 1338):

Dr. Cohen began by restating the history of the proposed amendment. He said Mr. Jeremy Rifkin of the Foundation on Economic Trends proposed a revision to the NIH Guidelines after the controversy concerning the Wistar Institute's rabies vaccine field test in Argentina. This proposal was considered at the September, 1987 RAC meeting. As a result, a working group was established to develop a proposal. Dr. Cohen said the Working Group on International Projects met on February 1, 1988, and developed a proposal that was considered by the RAC on June 3, 1988. At that time, it was referred back to the Working Group for additional discussion and revision. The Working Group met on August 15, 1988, and recommended the following proposal (tab 1338):

> "The NIH Guidelines are also applicable to recombinant DNA projects done abroad:
>
> "1. If they are supported by NIH funds; or
>
> "2. If they involve deliberate release into the environment or testing in humans of materials containing recombinant DNA developed with NIH funds, and if the

institution that developed those materials sponsors or participates in those projects. Participation includes research collaboration or contractual agreements, but not mere provision of research materials.

"If the host country has established rules for the conduct of recombinant DNA projects, then the project must be in compliance with those rules. If the host country does not have such rules, the proposed project must be reviewed by an NIH approved IBC or equivalent review body and accepted in writing by an appropriate national governmental authority. The safety practices to be employed abroad must be reasonably consistent with the NIH Guidelines."

Dr. Cohen said this proposal was published in the Federal Register and attempts to accomplish several things. It defines which of the international activities it does and does not affect. The first group pertains to projects supported by NIH funds, and the second group are projects involving deliberate release or human gene therapy experiments. The proposed language also makes it clear that the mere provision of research materials does not imply participation. Finally, the proposal addresses the presence or absence of guidelines in the host country.

Dr. Cohen said the intention of the proposed amendment was to provide guidance to researchers who develop potentially useful vaccines, treatments, or microorganisms so that responsible international projects in controversial areas such as deliberate release or human gene therapy can proceed with the knowledge and approval of the host country.

Dr. Atlas reminded the participants that debate at the last RAC meeting had centered around the terms "connected" and "direct extension of research." The Working Group then developed a sense of what the words "participation" and "responsibility" meant and to clarified the issue surrounding exchange of scientific materials. He said there was concern also as to how review committees could be established for looking at such problems, but that international IBCs exist in some countries. Where they do not, it was feasible for IBCs at U.S. institutions to accomplish such reviews rather than forcing every foreign country to establish an IBC to comply with the NIH Guidelines.

Dr. Clewell said he agreed with both Drs. Cohen and Atlas as to the aims of the proposed amendment. An effort was made to define what was meant by "extension of research" done domestically with NIH funds and the issue of "acceptance by an appropriate

government authority" meaning approval by an NIH recognized IBC. These points added strength to the proposal.

Mr. Lanman, who had just joined the group, said he supported the proposal. He said it was clear, sets a reasonably enforceable guideline, and is fairly consistent with what was originally proposed.

Dr. Pramer said he believed the Working Group was able to develop language which would cover situations similar to the Wistar incident while at the same time not constraining exchange of scientific material and keeping the number of reviews for such proposals to a minimum.

Dr. Riley supported the proposal and said the ambiguities and problems in phraseology which were discussed at the last RAC meeting had been resolved.

Dr. Davis said he felt the scientists and lawyers in the Working Group had taught each other something about the language, and he was happy with the product.

Dr. Childress asked for clarification of changes from the existing NIH Guidelines which appeared to be omitted from the new language. He said it appeared that a proposal could be reviewed by an NIH approved IBC and accepted in writing by an appropriate national governmental authority without notification to NIH that this process had taken place. Secondly, there was no mention of sanctions in the new language, which is defined by another section of the NIH Guidelines, and may not be explicit enough.

Dr. Cohen said there was no need to repeat the sanctions in this section since they were already in the NIH Guidelines. As for the notification of NIH, Dr. Cohen explained this was the responsibility of the institution and the researcher. It was not necessary to provide such information to the NIH.

Dr. Shibley asked for clarification of the meaning "equivalent review body." Dr. Cohen said the implication was that an IBC or an equivalent body functioning as a review body would approve the proposals. This could be a local IBC.

Dr. Shibley said that in the case of an experimental biologic, it would need not only IBC approval but would also require U.S. Department of Agriculture (USDA) approval for export. Dr. Cohen said the NIH Guidelines did not conflict with this in any way. Dr. McGarrity said the proposed amendment did not usurp the authority of any other Federal regulatory agency in this country or abroad, and it does not imply that these are the only guidelines that must be followed.

Dr. McGarrity asked Mr. Lanman if such wording would have prevented the Argentine occurrence from happening. Mr. Lanman said he had not reviewed the situation recently, but he believed that it would have prevented the incident. Mr. Lanman noted that no mention of compliance with USDA rules was made in any version of the NIH Guidelines. Dr. Shibley said he felt the language should be clearer. In his opinion in the case of the Wistar experiment, the Wistar IBC could have approved the export of the vaccine to Argentina. Since Argentina had no IBC, the experiment would have taken place anyway.

Dr. Riley said she believed the IBC or equivalent body referred to in the proposed amendment was one located in the foreign country. Dr. Childress replied he did not believe it was limited to the foreign country but merely an IBC which met NIH standards. Dr. Cohen said he agreed with Dr. Childress' interpretation.

Dr. Atlas said in the case of a Wistar IBC approving the experiment, it would still require "acceptance in writing by an appropriate national governmental authority," that was missing in the Wistar scenario. Dr. Shibley said it was not clear whether "national governmental authority" referred to a foreign government or a domestic governmental authority. If the latter were true, Wistar's IBC could approve the experiment, USDA could approve export, and the Argentinean government would still be unaware of the experiment.

Dr. Davis suggested adding the words "of the host country" after the word "authority" in the final paragraph for clarification.

Dr. Atlas moved adoption of the proposed amendment of Section I-C of the NIH Guidelines with the addition of the phrase "of the host country" after the word "authority" in the final paragraph. Dr. Cohen seconded the motion.

Dr. McGarrity asked if there was discussion on the motion. Dr. Warren Cheston of the Wistar Institute said the Institute would support these NIH Guidelines enthusiastically.

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed unanimously with 20 in favor 0 opposed, and no abstentions. Dr. McGarrity then called on Dr. Vidaver to present the next agenda item.

V. PROPOSED AMENDMENT OF SECTION I-B (TABS 1332/III, 1339, 1342):

Dr. Vidaver proposed the following suggested statement be added to Section I-B of the NIH Guidelines:

"Unmodified transposons (wild-type) that become inserted into a genome, even if carried by a recombinant vector or plasmid, are not subject to these Guidelines. For example, it is common to use vectors that either are naturally unstable (suicide vectors) in a desired host or that can be rendered unstable by manipulating physiological conditions. In the process of suicide (inability of the vector to replicate), transposon transfer may occur. This process is not considered recombinant DNA."

Dr. Vidaver said the amendment was proposed because of a definitional problem of what constitutes recombinant DNA. She said this had come into question in the case of a suspected violation of the NIH Guidelines by an investigator who released a bacterium into the environment that had enhanced fungicidal activity generated by transposon mutagenesis via a recombinant plasmid vector. However, the recipient bacterium contained only the unmodified transposon from the vector.

Dr. Vidaver said two comments had been received that offered amendments to wording of the proposed amendment. The first, from Dr. John Payne of USDA's Animal and Plant Health Inspection Service, proposed adding the following language to the end of the first sentence of the proposed amendment:

"...if the recombinant vector or plasmid are no longer present in the cell."

Dr. Vidaver said this would be accepted by her as a "friendly amendment," if it were so moved, with the exception that she would rather replace the word "if" at the beginning of the suggested amendment with the words "provided that."

Dr. Vidaver said tab 1342 was a letter from Dr. Jack J. Manis of the Upjohn Company who proposed adding the following paragraph to the proposed amendment:

"Likewise, strains resulting from the deletion of a recombinant transposon or exchange of a recombinant transposon for a wild type transposon via site-specific or homologous recombination are not considered to be recombinant and are not covered by these Guidelines."

Dr. Vidaver said she favored the addition presented by Dr. Manis. however, Dr. Vidaver did not want her original proposal to be impeded by the wording of this addition and said she preferred this to be a separate issue from the original proposal.

Dr. Riley supported the proposal including the modification by Dr. Payne. However, Dr. Riley said she could not agree with the

addition of the language presented by Dr. Manis in his letter because of conditions contained in the language which have been previously considered and still remain unresolved.

Dr. Erickson said he would have no trouble with the proposed amendment if it were applied only to plants and bacteria; however, he noted that mammalian biologists could consider retroviruses as transposons and said he would not like to have experiments with retroviruses be excluded from the NIH Guidelines.

Dr. Vidaver asked if such experiments would meet criteria for being recombinant DNA. Dr. Erickson said cells could be infected by a retrovirus carried in a new plasmid or vector and cause a burst of mutagenesis or activation of intrinsic retroviruses and be excluded from review under the NIH Guidelines if this proposed amendment was in place.

Dr. Roberts said that stipulating the plasmid has to be out of the cell is not necessary since that is already defined as recombinant DNA. What should be of concern is the definition of "recombinant DNA" as opposed to the fate of the cells in which an experiment is performed. He added he did not believe retroviruses were technically transposons and did not think anyone would try to interpret them as such.

Dr. Gellert supported Dr. Erickson and mentioned the discussions of the RAC relative to transgenic animals where much the same issues were discussed relative to the introduction of "stable recombinant DNA, or DNA derived therefrom." Dr. Gellert said this was a case where it was possible to insert "DNA derived therefrom" without its being literally recombinant and thus be excluded from review under the NIH Guidelines.

Dr. Elizabeth Milewski of the Environmental Protection Agency (EPA) asked Mr. Lanman for his opinion on how changes in definitional language would affect interagency coordination of efforts. Mr. Lanman said he believed all agencies involved should be working with the same definitions and asked Dr. Milewski whether EPA had developed a definition for recombinant DNA. She replied EPA was operating under a policy statement. Their language defining recombinant DNA was DNA that was "intergeneric," coming from organisms classified in different genera, in order to fall under EPA regulation. She said she was not familiar enough with biological issues of transposons to know if that would have an impact on the EPA definition.

Dr. Davis said he was surprised that a virus could be called a transposon. Dr. Erickson said in many instances journal articles have referred to retroviruses as "mammalian transposons." He suggested clarifying language be added to the proposed amendment

such as, "unmodified transposons (wild-type) of plants and bacteria that become inserted...." Dr. Roberts suggested retroviruses simply be excluded and added they are sometimes referred to as retroposons instead of transposons.

Mr. Mannix asked if by excluding retroviruses from the definition of what is not recombinant DNA would result in their being considered recombinant DNA. Dr. Roberts agreed that it was a problem, but a practical solution may be to exclude retroviruses.

Dr. Cohen asked whether it might not be better to list such experiments as exempt and simply add the proposed wording to Section III-D of the NIH Guidelines rather than attempting to change the definition of "recombinant DNA." Dr. Vidaver said she had no quarrel with such a proposal.

Mr. Mannix said he did not believe the intent of the proposal was to change the definition of "recombinant DNA," but that by listing it as an exemption it would be saying, by implication, that it had been included in the original definition. He said he would rather keep it as a clarification of what has always been the definition of "recombinant DNA."

Dr. Vidaver said her original thinking was that it be a footnote. She had no quarrel with where it was inserted, but it should be made explicit somewhere in the NIH Guidelines.

Dr. McGarrity suggested that Dr. Vidaver and interested members meet at the afternoon coffee break and formulate a revised proposal and bring it back with concrete suggestions as to where it should be placed in the NIH Guidelines. He then recessed the Committee for the afternoon coffee break asking them to return at 2:45 p.m.

Dr. McGarrity called the final session to order and called on Dr. Vidaver to continue discussion of the proposed amendment to Section I-B of the NIH Guidelines.

Dr. Vidaver said an ad hoc committee of interested RAC members had devised the following substitute proposal to be considered as a clarifying statement in Section I-B of the NIH Guidelines:

> "Genomic DNA of plants and bacteria that has acquired an unmodified (wild-type) transposable element, even if the latter was donated from a recombinant vector no longer present, is not subject to these Guidelines."

Dr. Vidaver noted this statement is restricted to plants and bacteria and allows for dealing with animal issues at a later time. Drs. Gellert and Erickson said this would meet with their approval. Dr. Roberts said the parenthetical expression of

"(wild-type)" should be removed. If it were not such, it would be classified as a recombinant covered by other sections of the NIH Guidelines.

Dr. Payne said removing "wild type" would imply that all transposons were not recombinant even if the transposon itself was recombinant. Dr. Roberts said the words "bacterium, phage, and cell" needed no qualifiers except in the case of their being recombinants, and natural mutations were not to be treated as recombinant DNA.

Mr. Mannix suggested striking the words "wild type" and adding the following to the end of the first sentence:

> "...unless the transposon contains DNA segments that are otherwise recombinant as defined in the preceding paragraph."

Dr. Vidaver said she had no quarrel with this suggestion and read the proposed amended wording:

> "Genomic DNA of plants and bacteria that has acquired a transposable element, even if the latter was donated from a recombinant vector no longer present, is not subject to these guidelines unless the transposon itself contains recombinant DNA."

Dr. Roberts moved approval of this amendment to Section I-B of the NIH Guidelines. Mr. Mannix seconded the motion. Dr. Roberts asked where Dr. Vidaver proposed the paragraph to appear, and she said she saw it as a separate paragraph at the end of Section I-B in the NIH Guidelines.

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed by a unanimous vote.

Dr. McGarrity thanked Dr. Vidaver and called on Dr. McKinney to present the next agenda item.

VI. DISCUSSION OF SHIPMENT OF rDNA MOLECULES (TABS 1335, 1340):

Dr. McKinney said the U.S. Postal Service proposed changing their regulations relative to mailing of etiologic agents in June of this year in a proposal entitled "The Non-Mailability of Etiologic Agents." He said it occurred to him that the present wording of the NIH Guidelines in Appendix H states, "Recombinant DNA molecules contained in an organism or virus shall be shipped only as etiologic agents." This has not been amended since 1976, despite the acquisition of new knowledge of recombinant molecules

and host organisms and is not current with the rest of the NIH Guidelines.

Dr. McKinney said there are a number of experiments which fall in the "Exempt Category" as well as a number of experiments which do not require filing a registration document with the IBCs and others where IBC filing and approval are required. This caused Dr. McKinney to propose to ORDA that RAC create a subcommittee to study the issue of Appendix H so that it can be updated and made current with the rest of the NIH Guidelines in terms of the characterization and classification of recombinant molecules.

Dr. McKinney said while there are a number of organisms exempt for research purposes, they may not be exempt for mailing. A balance must be maintained between what is acceptable for mailing and in what form. There may be cases where a recombinant is acceptable for mailing and the host molecule may not be, or vice versa. He said a review of this would be challenging, but it was clearly something that would aid the technology as well as investigators.

Dr. McKinney said one comment had been submitted in the form of a proposed draft from the Advisory Committee to the U.S. Department of Commerce. Dr. Robert Stevenson was present and may wish to address the issue. Dr. McGarrity said he would give Dr. Stevenson a chance to comment after the primary and secondary reviewers.

Dr. Musgrave said the U.S. Postal Service determines what markets it wishes to serve, and this should not be a driving force in decisions made by the RAC as to issues of mailability. He said the issue has to do with interagency regulations between the U.S. Departments of Transportation and Health and Human Services, rather than involving the Postal Service. He did not believe changes were necessary in labeling to suit one vendor of services.

Dr. McGarrity said there was concern that if the Postal Service refused acceptance of materials that perhaps private carriers would do the same. Dr. Musgrave reiterated that it was only in the best interest of the industry to ensure that there was no mislabeling and no danger in mailing. Whether the Postal Service chooses to meet a particular market should not be of concern to the Committee. Dr. McKinney said this was true, but many of the private mail carriers follow the policies of the Postal Service to a large extent. In fact, the Airline Pilot's Association regulations are more restrictive than the Postal Service.

Dr. McKinney said changes in Appendix H might help alleviate some problems of shipping significant quantities of agents for potential agricultural use which are restricted at present.

Dr. Murray said he did not find a definition for "etiologic agent" in the NIH Guidelines, and a definition would be necessary to effectively deal with any issues of mailability or transportation.

Dr. Gellert said alternative shippers could be found but the price was the practical matter. If the Postal Service definitions are accepted, the rates for shipping could escalate if nothing is done about defining an "etiologic agent." Mr. Mannix said "etiologic agent" may cover too many things and that a differentiation must be made as to what types of products were actually being shipped.

Dr. Davis said the concept and definitions of "etiologic agents" are being distorted in order to please the Postal Service or make it willing to accept these materials, and this is not the real issue. The issue is that much has been learned about recombinant DNA. The language in Appendix H does not reflect this accrued knowledge. If this is not corrected, it would reinforce the public myth that, "all bugs and germs are dangerous."

Dr. Atlas said he thought it in the best interests of the scientific community to let the Postal Service finish formulating its policy on etiologic agents, and then it would be the responsibility of the community to educate the Postal Service as to which microbes are dangerous and which are not. The point then can be made that perhaps recombinant molecules are not "etiologic agents," in the same sense as some dangerous microbes or other materials.

Dr. McGarrity cautioned the Committee that nothing could be done to effect changes in the NIH Guidelines at this meeting. A proper notice and Federal Register publication would be required before action could be taken.

Dr. Musgrave said he agreed that proper labeling was the real issue. The concern of the Committee should be scientific evidence of danger and not issues of the transportation system.

Dr. Sue Tolin, USDA, said she was disturbed by the Postal Service definition of "etiologic agent" as those agents that cause only diseases in humans and said she believed clarification was necessary to ensure that agents toxic to plants are somehow looked at as "etiologic agents."

Dr. McKinney said he had spoken with Dr. McVicar of the Centers for Disease Control (CDC). The CDC is responsible for parts of the regulation dealing with shipment of etiologic agents and other biologic materials. Dr. McVicar informed him that CDC is in the process of writing definitions. This would afford the RAC

a chance for informal input in the process before a new regulation is published for public comment. Such cooperation could allow the development of language in the proposed regulation that could merely be adopted by reference into the NIH Guidelines.

Dr. Davis proposed a resolution that it was the sense of the Committee that it would be desirable to revise the definition of recombinant organisms in such a way that recognizes that a very large class are now exempt from being considered etiologic agents. Dr. Musgrave seconded the resolution.

Dr. McGarrity called for further discussion and asked Dr. Stevenson for any comments. He reported that the congressional committee with jurisdiction over the Post Office was meeting on October 5 to discuss the whole issue of shipment of etiologic agents. Dr. Stevenson also noted that he is the chairman of the Biotechnology Technical Advisory Committee at the Department of Commerce. His Committee had been trying to loosen export control procedures for common microorganisms of Class 2 and below. They had received information from several Federal agencies that genetically engineered organisms would be subject to individual specific export control applications and would require specific documentation for export outside the continental United States. He said he felt this would be expensive and troublesome. He stated further that when the Human Genome project gets under way, some 3,000 cosmids may appear on the scene to provide an additional paperwork burden. He said a working definition that can be used by the layman in the bureaucracy to differentiate between what is and is not dangerous and labels for proper shipment needs to be developed.

Dr. Stevenson reported that over 600 comments had been received by the Postal Service on this subject. The major concern is potential cost of shipping. Those most affected would be clinical laboratories who would have to ship all urine and blood samples by courier causing the cost of medical diagnosis to rise substantially.

Dr. Musgrave asked if there was any evidence that United Parcel Service (UPS) had refused any shipments. Dr. Stevenson said this had occurred. He would furnish Dr. Musgrave with a letter describing such instances, and a general procedure in which UPS states they will not accept any infectious agents whatsoever. Dr. Musgrave said this could be another issue of mislabeling, and smart carriers will learn efficient methods of shipping materials at competitive prices.

Dr. Musgrave asked for a re-reading of the motion. Ms. Levinson restated the motion as:

"It is desirable to revise the definition of recombinant organisms in a way that recognizes our awareness that there is a very large body of organisms that are exempt."

Dr. Murray said he believed the phase "...that would not be considered etiologic agents...." was in the original motion. Dr. Erickson said he believed the word "exempt" was used but he preferred Dr. Murray's wording. The maker of the motion and the second agreed this wording should be incorporated to make the resolution read:

"It is desirable to revise the definition of recombinant organisms in a way that recognizes our awareness that there is a very large body of organisms that would not be considered etiologic agents."

Dr. McKinney asked whether a new subcommittee would be formed to deal with this matter. Dr. McGarrity said there were four standing subcommittees at present. Perhaps the Subcommittee on Definitions could be restructured or augmented in some way to handle this matter. Dr. McKinney reiterated Dr. McVicar's willingness to work with the RAC.

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed unanimously.

VII. FUTURE MEETING DATES:

Dr. McGarrity called the Committee's attention to the future meeting dates and noted the next meeting would take place on January 30, 1989, with meetings scheduled on June 5, 1989, October 6, 1989, and a new date for February 5, 1990. He advised members of the Committee to mark their calendars with these dates. He also noted the ORDA office would be moving back to the NIH campus and members would be advised of the new mailing address.

VIII. ADJOURNMENT:

Dr. McGarrity thanked all members of the Committee and others present for their participation and adjourned the meeting at 3:25 p.m. on October 3, 1988.

Respectively submitted,

Rachel E. Levinson
Rapporteur

Jay Moskowitz, Ph.D
Acting Executive Secretary

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachment are accurate and complete.

Date

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